

U.S. Application No. 10/788,728
Attorney Docket No.: 31869.703.201
(formerly WFRST.006C1)

REMARKS

Claims 1, 3, 5, 14 are amended herein, and claims 2, 4, 6-13, and 15-17 are cancelled herein. Upon entry of these amendments, claims 1, 3, 5, 14, 18, and 19 are pending. The foregoing claim amendments do not constitute any admissions of patentability regarding the present invention. Applicants reserve the right to pursue future continuing applications directed towards claims not presented herein.

The amendments to the claims do not add new matter. The amendment to claim 1 introduces recitation from originally filed claim 2. Additional support for claim 1 can be found throughout the specification, such as on p. 1 at [0006].

The amendment to claim 3 recites dependency on amended claim 1.

The amendment to claim 5 recites dependency on amended claim 3. Support for claim 5 can be found throughout the specification, such as on p. 5 at [0020], p. 6-7 at [0028], and p. 7-8 at [0030].

The amendment to claim 14 recites proper antecedent basis, dependency on amended claim 1, and recites compounds. Support for claim 14 can be found throughout the specification, such as on p. 2 at [0009].

The amendment to the specification does not add new matter. As required by the Examiner, the amendment to paragraph [0043] renumbers Example 2 as Example 3.

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I. Objections Relating to Claim Informalities

The objection to claims 4 and 10 is rendered moot in light of the amendment herein canceling claims 4 and 10.

The objection to claim 14 for misspelling a compound name is rendered moot in light of the amendment removing the subject word from the claim recitation.

II. Rejection Under 35 U.S.C. § 112, ¶1- Written Description

Claims 1-8, 10-12, and 16-17 are rejected under 35 U.S.C. § 112, ¶1 for allegedly failing to comply with the written description requirement.

Specifically, the Examiner asserts that "there is **no general structural chemical formula for the intermediate compound** which describes distinguishing identifying characteristics sufficient show that the applicant was in possession of the claimed invention..." [See Office Action at page 4, paragraph 2; emphasis added in bold.]

As amended herein, claim 1 is drawn to methods for preparing a compound of formula 1 by selectively reducing the nitrile moiety of recited intermediate compounds corresponding to a specified structural chemical formula. Thus, the rejection of claim 1 is obviated in light of the amendment and withdrawal is respectfully requested.

Since claims 2, 4, 6-8, 10-12 and 16-17 are canceled herein, the rejection of these claims is rendered moot.

III. Rejection Under 35 U.S.C. § 112, ¶1- Scope of Enablement

Claims 1-8, 10, and 11 are rejected under 35 U.S.C. § 112, ¶1 for alleged lack of enablement over the scope of the claims.

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The Examiner alleges that "this description does not reasonably provide enablement for any or all the compounds containing fluorine and a nitrile moiety known in the art." In particular, the Examiner asserts that "the specification falls short because data essential for how any intermediate compound containing fluorine and a nitrile moiety would lead to the desired final product..." [See Office Action at pages 6-7.] Applicants respectfully disagree.

As amended herein, claim 1 is drawn to methods for preparing a compound of formula 1 by selectively reducing the nitrile moiety of intermediate compounds *corresponding to a specified structural chemical formula*. Contrary to the Examiner's assertions, the specification provides sufficient guidance so as to enable one of ordinary skill in the art to practice the claims as amended herein. Specifically, the specification provides guidance about various processes to synthesize compound 1 by employing intermediate compounds of a specific structure and chemical formula 12, as provided in claim 1. As illustrated in Examples 1-6, the specification provides representative synthetic routes for preparing compound 1. The specification also provides sufficient guidance to enable one of ordinary skill to make and use intermediate compounds that can be employed in preparing compound 1.

Because the specification provides sufficient guidance to enable one of ordinary skill to practice the claims, Applicants respectfully assert that the rejection on this basis is obviated in light of the amendments presented herein. Withdrawal is respectfully requested.

IV. Rejection Under 35 U.S.C. § 112, ¶2- Indefiniteness

Claims 1-11 are rejected under 35 U.S.C. § 112, ¶1 for alleged indefiniteness.

A. Claim 1

Regarding claim 1, the Examiner asserts that the phrase "an intermediate compound comprising fluorine and a nitrile moiety" is vague. [See Office Action at page 17, paragraph 3.] Because amended claim 1 provides a structural chemical formula corresponding to the recited

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intermediate compounds, Applicants respectfully assert that the recitation of claim 1 is clear. Applicants respectfully request withdrawal of the rejection.

B. Claims 1, 4, and 10

Regarding claims 1, 4, and 10, the Examiner asserts that these claims omit essential steps about

how selectively the nitrile is reduced under particular reaction conditions such as specific temperature range (25 to 40° C) and pressure range (80 to 120 psi), and the use of a specific reagent (hydrogen) and catalyst (transition metal catalyst: palladium on carbon). [See Office Action at page 17, paragraph 4- page 18, paragraph 1.]

Applicants respectfully assert that the Examiner's rejection is inappropriate because the claims recite all of the elements necessary to practice the invention.

"A claim which omits matter disclosed to be essential to the invention as described in the specification or in other statements of record may be rejected under 35 U.S.C. 112, first paragraph, as not enabling. Such essential matter may include missing elements, steps or necessary structural cooperative relationships of elements **described by the applicant(s) as necessary to practice the invention.**" [See MPEP 2172.01 citing *In re Mayhew*, 527 F.2d 1229; emphasis added in bold.]

"In determining whether an unclaimed feature is critical, the entire disclosure must be considered. **Features which are merely preferred are not to be considered critical.**" [See MPEP 2164.08(c) citing *In re Goffe*, 542 F.2d 564; emphasis added in bold.]

"An enablement rejection based on the grounds that a disclosed critical limitation is missing from a claim should be made **only when the language of the specification makes it clear that the limitation is critical for the invention to function as intended.** Broad language

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in the disclosure, including the abstract, omitting an allegedly critical feature, tends to rebut the argument of criticality.” [See MPEP 2164.08(c); emphasis added in bold.]

On a first note, Applicants point out that the Examiner has rejected claims 1, 4, and 10 under 35 U.S.C. 112, second paragraph for alleged indefiniteness. As stated in the MPEP, claims that omit essential steps should be rejected under 35 U.S.C. 112, first paragraph for lack of enablement. Secondly, claims 4 and 10 are cancelled by amendment herein and thus, the rejection of these claims is rendered moot.

With respect to claim 1, Applicants respectfully assert that the claim recites at least all of the elements that are necessary to practice a process for preparing compound 1 by selectively reducing the nitrile moiety of compounds of formula 12. Claim 1 recites the structural chemical formula of intermediate compounds employed in the synthesis of compound 1. In addition, the specification describes multiple embodiments for preparing compound 1 (e.g., Examples 1-6). For example, the specification describes various reaction conditions, such as representative temperature ranges (e.g., page 3 at [0013]), representative catalysts (e.g., page 4 at [0015], page 5 at [0021]), representative reagents (e.g., page 4 at [0016] - [0019]), etc., for performing the claimed methods. By requiring the claim to recite specific temperature ranges, pressure ranges, and specific catalysts, the Examiner has inappropriately and incorrectly treated preferred features disclosed in the specification as being critical.

Accordingly, Applicants respectfully assert that the Examiner has failed to establish a *prima facie* case of indefiniteness, and withdrawal of this rejection is respectfully requested.

C. Claims 4 and 5

Regarding claims 4 and 5, the Examiner asserts that the phrase “a compound comprising an ester or amide” renders the claims vague and indefinite. [See Office Action at page 18, paragraph 2.] Claim 4 is cancelled herein and claim 5 has been amended to remove the subject phrase and recite compounds corresponding to specified formulas. Therefore, the rejection on this basis is rendered moot and withdrawal is respectfully requested.

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D. Claim 6

Regarding claim 6, the Examiner asserts that the phrase "a compound comprising fluorine and a moiety" renders the claim vague and indefinite. [See Office Action at page 18, paragraph 3.] Claim 6 is cancelled herein and therefore, the rejection is rendered moot. Withdrawal is respectfully requested.

E. Claim 7

Regarding claim 7, the Examiner asserts that the phrase "said intermediate compound contains at most one Schiff's base" renders the claim vague and indefinite. [See Office Action at page 18, paragraph 4.] Claim 7 is cancelled herein and therefore, the rejection is rendered moot. Withdrawal is respectfully requested.

F. Claim 9

Regarding claim 9, the Examiner asserts that the phrase "Z is (ii) a moiety" renders the claim vague and indefinite. [See Office Action at page 19, paragraph 1.] Claim 9 is cancelled herein and therefore, the rejection is rendered moot. Withdrawal is respectfully requested.

G. Claim 10

Regarding claim 10, the Examiner asserts that the phrase "an intermediate compound comprising fluorine and a nitrile moiety" renders the claim vague and indefinite. [See Office Action at page 19, paragraph 2.] Claim 10 is cancelled herein and therefore, the rejection is rendered moot. Withdrawal is respectfully requested.

V. Rejection for Obviousness-type Double Patenting

Claims 1-19 are rejected under for alleged obviousness-type double patenting over claims 1-3, 6-7, 11, 14, 20-23, and 33 of U.S. Patent No. 6,730,809.

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The Examiner asserts that the claims are not "patentably distinct from each other because U.S. Patent No. 6,730,809 B2 does disclose a process for the production of alpha-difluoromethylornithine (DFMO) by selectively reducing a nitrile moiety and further hydrolyzing the remaining product to produce the desired alpha-difluoromethylornithine product..." [See Office Action at page 20, paragraph 1.] The Examiner further alleges that U.S. Patent No. 6,730,809 discloses that "the specific temperature range of -35° to 25° C in the alkylation reaction is a crucial parameter on the way to accomplishing the production of alpha-difluoromethylornithine." [See Office Action at page 28, paragraph 1.] Applicants respectfully disagree.

The amended claims recite the structural chemical formula of various intermediate compounds employed in the synthesis of compound 1. As discussed above in Section IV(B), the specification describes multiple embodiments for the synthesis of compound 1 (e.g., Examples 1-6). Additionally, the specification describes numerous reaction conditions including, for example, *representative* temperature ranges under which to perform *an exemplary* alkylation reaction of *an embodied intermediate*, compound 4. "The alkylation reaction is carried out, for example, by deprotonation at a temperature of from **about -35 to about 25° C.**" [See Specification at page 4, [0018]; emphasis added in bold.]

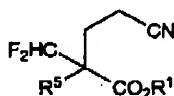
Contrary to the Examiner's allegation that "the specific temperature range of -35° to 25° C in the alkylation reaction is a crucial parameter on the way to accomplishing the production of alpha-difluoromethylornithine," the specification explicitly describes the alkylation reaction of compound 4 at the temperature range of -35° to 25° C as an exemplary embodiment. Moreover, the specification describes other intermediate compounds, in addition to compound 4, which may be employed in the preparation of the title compound, such as compound 5 (described in Schemes 2 and 4 of the specification), and compound 6 (described in Schemes 3 and 5 of the specification). Although Applicants respectfully disagree with the obviousness type double patenting rejection, Applicants have filed a terminal disclaimer with this Response under separate cover in an effort to expedite prosecution. Accordingly, withdrawal of this rejection is respectfully requested.

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VI. Rejection Under 35 U.S.C. § 102(b)- Anticipation

Claims 6, 7, 9, and 18-19 are rejected for alleged anticipation by Bey *et al.* (J. Am. Chem. Society, 100: 2551-2553 (1978)). Specifically, the Examiner alleges that "Bey et al discloses the synthesis of alpha-difluoromethylornithine (DFMO) by regioselective alkylation of the Shiff base of ornithine methyl ester with chlorodifluoromethane and subsequent acidic hydrolysis." [See Office Action at page 29, paragraph 2.] In particular, the Examiner alleges that Scheme II on page 2552, right column, first paragraph in Bey *et al.* is "identical with the claims."

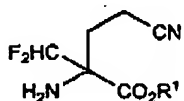
First, claims 6, 7, and 9 are cancelled herein and thus, the rejection with respect to these claims is rendered moot. Claims 18 and 19 are drawn to compounds of the formula



wherein R¹ is linear or branched C₁ to C₄ alkyl (such as methyl, ethyl, and t-butyl), and R⁵ is:

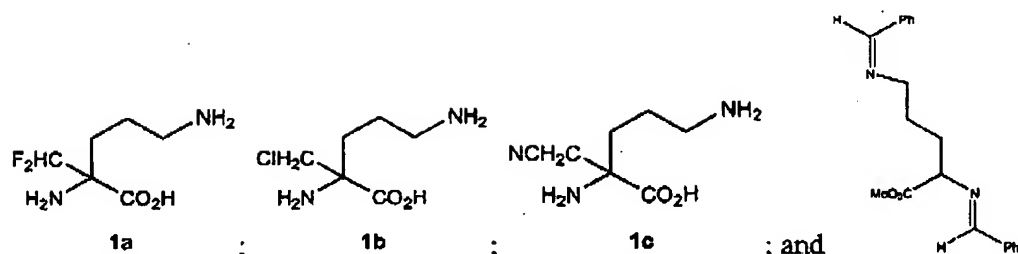
- (a) R2-C(=N)c1ccccc1, wherein R² is hydrogen, linear or branched C₁ to C₄ alkyl or aryl;
- (b) NH₂; or
- (c) NC(=O)R4, wherein R⁴ is linear or branched C₁ to C₄ alkyl, alkoxy or aryl.

Thus, in a representative embodiment where R⁵ is NH₂, claims 18 and 19 would be directed to compounds corresponding to:



In contrast to the compounds claimed herein, Scheme II in Bey *et al.* discloses the following compounds:

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As illustrated above, compounds disclosed in *Bey et al.* are not identical with compounds recited in claims 18 and 19. Thus, the presently claimed compounds are not anticipated by *Bey et al.* Because the Examiner has failed to establish a *prima facie* case of anticipation, Applicants respectfully request withdrawal of the rejection on this basis.

VII. Rejection Under 35 U.S.C. § 103(a)- Obviousness

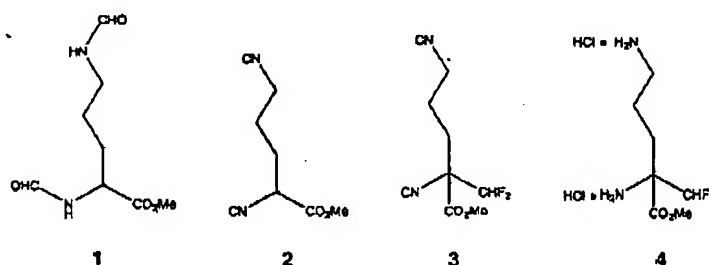
Claims 1, 2, 4-6, 9, 10, 12, 16, 18, and 19 are rejected under 35 U.S.C. § 103(a) for alleged obviousness over *Seki et al.* (*Biosci. Biotech. Biochem.*, 57(6): 1024-1025 (1993)).

The Examiner alleges that *Seki et al.* "discloses a preparation of alpha-difluoromethylornithine (DFMO) from OrnOME-2HCl by using an diisocyanato intermediate prepared via the formyl derivative and alkylated with ClCHF₂ followed by acid hydrolysis..." [See Office Action at page 30, paragraph 4- page 31, paragraph 1.] In addition, the Examiner asserts that "instant invention, however, differs from the prior art in that the final claimed compound has no hydrochloride salt form unlike the prior art compound." [See Office Action at page 31, paragraph 2.] Applicants respectfully assert that *Seki et al.* fails to teach or suggest all of the limitations recited in the present claims. Specifically, *Seki et al.* fails to teach or suggest intermediate compounds corresponding to formula 12 in the preparation of compound 1.

"To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art." [See MPEP 2143.03 citing *In re Royka*, 490 F.2d 981; emphasis added in bold.]

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Seki *et al.* does not teach or suggest the preparation of compound 1 using any of the intermediate compounds recited in claim 1. Seki *et al.* provides only one synthetic route producing the hydrochloride salt of alpha-difluoromethylornithine (annotated as compound 5 in Seki *et al.*). The route in Seki *et al.* employs the hydrochloride salt of L-ornithine-OMe and the following intermediates:



As illustrated above, it is evident that the intermediates provided in Seki *et al.* do not correspond to any of the compounds currently claimed. Because Seki *et al.* fails to teach or suggest all of the limitations recited in the claims, Applicants respectfully assert that claims 1, 2, 4-6, 9, 10, 12, 16, 18, and 19 are non-obvious over the cited reference. Withdrawal of the rejection on this basis is respectfully requested.

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CONCLUSION

Applicants respectfully solicit the Examiner to expedite prosecution of this patent application to issuance. Should the Examiner have any questions, the Examiner is encouraged to telephone the undersigned.

The Commissioner is hereby authorized to charge any additional fees that may be required, or credit any overpayment to Deposit Account No. 23-2415 (Attorney Docket No. 31869-702.201).

Respectfully submitted,

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